

# Thymic Epithelial Neoplasms: A Comprehensive Review of Diagnosis and Treatment

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Cesar A. Moran and Saul Suster

### Histologic Classification of Thymoma: The World Health Organization and Beyond

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Saul Suster and Cesar A. Moran

Thymoma classification has remained for many years a troubled and contentious field. In recent years, the World Health Organization (WHO) presented a proposal for the histopathologic classification of thymic epithelial neoplasms that has been adopted as the standard by many pathologists throughout the world. Yet, controversy still exists regarding its validity, accuracy, usefulness, and reproducibility in routine clinical practice. This article reviews the basic criteria of the current WHO classification of thymoma, along with its weaknesses and limitations, and presents alternate proposals for the histopathologic approach to the classification of thymic epithelial neoplasms.

### Thymic Carcinoma: Current Concepts and Histologic Features

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Cesar A. Moran and Saul Suster

Thymic carcinoma is a rare tumor that has traditionally posed a significant challenge for diagnosis to clinicians and histopathologists. No reliable histopathologic features have yet been identified that can permit reliable distinction of these tumors from a metastasis to the mediastinum. Histologically, the tumors are characterized by morphologic features that are indistinguishable from those arising from a variety of other epithelial organs. A large number of histologic variants have been described. In general, these tumors remain a diagnosis of exclusion and, as a group, represent high-grade neoplasms with a very aggressive clinical behavior and an often-ominous prognosis.

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Melissa L. Rosado-de-Christenson, Diane C. Strollo,  
and Edith M. Marom

Thymic epithelial neoplasms are uncommon lesions. Affected patients may be asymptomatic or may present with thoracic complaints or paraneoplastic syndromes. Asymptomatic lesions may be discovered

incidentally during chest radiography or during other chest imaging studies. This article addresses the imaging evaluation of patients who have thymic epithelial neoplasms, specifically covering the use of chest radiography, CT, MRI, and positron emission tomography.

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Paul E. Wakley, Jr

Fine-needle aspiration (FNA) biopsy of thymoma is a demanding diagnostic exercise by the cytopathologist because of an overwhelming, often obscuring population of benign lymphocytes in many cases. Diagnosis requires the presence of a dual population of unequivocal epithelial cells and lymphocytes in the correct clinical-radiologic context. Cytologic examination alone is not insufficient to discriminate among the various subtypes of thymoma, nor can capsular invasion or invasion of adjacent structures be determined using FNA. The cytopathology of various thymic carcinomas (including neuroendocrine carcinoma) imitate their appearance in extra-thymic sites, and are generally recognizable using FNA. Separation of moderately differentiated neuroendocrine carcinoma from poorly differentiated small cell neuroendocrine carcinomas is generally not possible.

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Elisabetta Kuhn and Ignacio I. Wistuba

The etiology and molecular pathogenesis of thymic tumors are unknown. However, during the last two decades there has been some progress on elucidating the genetic abnormalities present and molecular pathways altered in thymic tumors. These abnormalities, while bearing distinctions and similarities to those described in other tumors, can be organized under the “hallmarks of cancer,” as proposed by Hanahan and Weinberg. These changes include self-sufficiency in growth signaling, insensitivity to antigrowth signals, ability to evade apoptosis, limitless replicative potential, ability to sustain angiogenesis, and tissue invasion and metastasis. However, this progress is still limited and has not led to better tumor classifications, prognostication of outcome, and design of molecular targeted therapy.

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Erin M. Casey, Patrick J. Kiel, and Patrick J. Loehrer, Sr

Thymoma and thymic carcinomas are rare epithelial tumors that arise from the thymus gland. Current management depends on staging, with surgery being the mainstay of therapy for stages I and II disease. Combined modality therapy, including radiation and chemotherapy, is recommended for patients who have invasive and metastatic disease. Relapse has been documented decades after initial therapy with options

for treating recurrent advanced stage disease. Prospective studies have been limited, and current studies aim to evaluate novel treatment options.

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Larry R. Kaiser

Resection continues to be the mainstay of treatment for epithelial lesions of the thymus. This has never been in doubt for encapsulated stage I and II lesions, but we recently have come to a greater appreciation of the role of preoperative therapy for locally advanced lesions, particularly stage III disease. For any lesion that presents in the anterior mediastinum and on CT scan does not appear to be eminently resectable, a biopsy should be performed to rule out lymphoma after serum germ cell markers have been obtained to rule out the rare primary mediastinal or metastatic germ cell tumor.

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Clifton David Fuller, Douglas M. Housman, and  
Charles R. Thomas

The role of radiotherapy for patients who have thymic neoplasms remains unclear. The low incidence of thymic malignancies, excellent outcome with complete resection, and limited body of evidence obfuscate the role of radiation therapy within the current multidisciplinary management of disease. Nonetheless, existing literature reports and novel radiotherapy techniques show increasing potential for integration of radiotherapy into the standard therapeutic milieu for carefully selected patient subpopulations.

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Laura M. Tormoehlen and Robert M. Pascuzzi

The relationship between myasthenia gravis and thymic pathology, including thymoma, is well known. Approximately 10% to 15% of patients who have myasthenia gravis are observed to have a thymoma. Myasthenia gravis may be considered as the most common of the paraneoplastic syndromes in patients who have thymoma. This article summarizes the clinical aspects of myasthenia gravis, followed by a review of the less often recognized paraneoplastic disorders noted to occur in patients who have thymoma.

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Mark R. Wick

The prognosis of thymic epithelial tumors depends on their separation into thymoma and thymic carcinoma, as well as the extent to which they involve adjacent tissues and organs. To formalize evaluations of

the latter attribute, several staging systems have been developed over the past 30 years. These include the Masaoka, Bergh, Wilkins-Castleman, Groupe d'Etudes des Tumeurs Thymiques, and tumor-nodal-metastasis schemes. The first of those formulations is most commonly employed in clinical practice, at least in the United States. The author believes that surgical-pathologic staging is the most powerful and reliable prognosticator for thymoma, as compared with histologic subtype-related prediction of behavior for that tumor type. Those topics, as well as affiliated issues concerning tissue sampling and staging techniques, are discussed in this article.

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Alberto M. Marchevsky, Robert J. McKenna, Jr,  
and Ruta Gupta

Evidence-based pathology promotes the critical evaluation of current clinical information and the development of evidence-based diagnostic and prognostic guidelines. No randomized clinical trials of patients who have thymomas or thymic carcinomas are available to evaluate the validity of the current World Health Organization (WHO) histologic classification or the widely used Masaoka staging system. A meta-analysis of over 2000 thymoma patients estimated that only three WHO histologic types of thymomas are associated with significant survival differences. Prospective randomized clinical trials and an international registry of patients who have Thymic epithelial neoplasms are needed to stratify patients who may benefit from neoadjuvant chemotherapy, postoperative radiation therapy, and other nonsurgical modalities.

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Alan Neibauer

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